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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KRISHNAN, GANAPATHY	

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1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,177	BONNAFFE ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35,40,42 and 44-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18-23* is/are allowed.

6)☒ Claim(s) *1-17 and 24-35, 40, 42 and 44-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 12/23/2008 has been entered.

The Request for Continued Examination filed 12/23/2008 has been carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 36-39, 41 and 43 have been canceled.

2. New Claim 51 has been added.

3. Claims 8, 25, 30-34, 40 and have been amended.

4. Remarks drawn to claim objections and rejections under 35 USC 112, first and second paragraphs and 103.

Claims 1-35, 40, 42 and 44-51 are pending in the case.

The rejection of claims 8, 30-31 and 40 under 35 USC 112, second paragraph of record in the previous office action, for recitation of the terms, 'for example', has been overcome.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-28, 30-34, 40, 45-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compound of formula (I) and the process of making it, does not reasonably provide enablement for the use of the said compounds in the treatment of the diseases and prevention of transplant rejection as recited in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The state of the prior art
(D) The level of predictability in the art
(D) The amount of direction provided by the inventor
(E) The existence of working examples
(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The instant claims are drawn to the use of the compounds of formula (I) for the treatment of autoimmune, inflammatory, degenerative diseases and preventing transplant rejection. The terms, autoimmune, inflammatory, degenerative diseases recited in the claims are extremely broad and are seen to include numerous disorders and conditions of which only a few are recited in the instant claims.

The state of the prior art

The examiner notes that the art cited by the applicants and used in the rejection below, teaches the use of carbohydrates for modulating the activity of γ-interferon. However, there is no teaching of the treatment or prevention of diseases and conditions in the prior art. One of ordinary skill in the art would not extrapolate the information in the prior art to the treatment of all of the said diseases and conditions encompassed by the broad recitations in the instant claims.

The level of predictability in the art

There is not seen sufficient data to substantiate the treatment of the said diseases and conditions or prevention of transplant rejection using the compounds of this invention. For example, autoimmune diseases are characterized by the body's immune responses being directed against its own tissues, causing prolonged inflammation and subsequent tissue destruction. Autoimmune disorders can cause immune-responsive cells to attack the linings of the joints--resulting in rheumatoid arthritis--or trigger immune cells to attack the insulin-producing islet cells of the pancreas leading to insulin-dependent diabetes. A healthy immune system recognizes, identifies, remembers, attacks, and destroys bacteria, viruses, fungi, parasites, and cancer cells or any health-damaging agents not normally present in the body. A defective immune system, on the other hand, wreaks havoc throughout the host by directing antibodies against its own tissues. Any disease in which cytotoxic cells are directed against self-antigens in the body's tissues is considered autoimmune in nature. Such diseases include, but are not limited to, celiac disease, Crohn's disease, glomerulonephritis, pancreatitis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, and other endocrinopathies. According to The Merck Manual (1992, pages 1488-1491 and pages 1684-1689) the cause of

multiple sclerosis is unknown even though immunologic abnormality is suspected and there is no clue to a specific mechanism. There is also no specific therapy (page 1490-see under Treatment). With regard to glomerulonephritis also no specific treatment is available. Immunosuppressive agents are ineffective and may even worsen the condition (page 1688-see under Treatment).

The diseases and conditions encompassed by the instant claims all have different etiologies and the said treatment using the compounds of the instant invention of all the diseases/conditions is highly unpredictable.

The amount of direction provided by the inventor

The instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure the treatment and prevention methods o all the disease/conditions as instantly claimed. The specification also fails to direct the skilled artisan in correlative prior art procedures which might provide the basis for the said treatment. Applicants state that (specification, page 18, last paragraph) that pro-inflammatory cytokines like IFN-γ are associated with several diseases. This does not mean that modulating IFN-γ alone would treat the disease/conditions as instantly claimed or prevent transplant rejection.

The existence of working examples

The working examples set forth in the instant specification are drawn to the synthesis of compounds of formula (I). There are no enabling disclosure/examples for the treatment of the disease/conditions as instantly claimed.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the use of the instant compounds for the treatment of the diseases/conditions and prevention of transplant rejection as instantly claimed. One of ordinary skill in the art would have to carry out experimentation in order to determine the efficacy of the said compounds in the said methods of treatment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25, 28, 30-34, 40 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25, 32-34 and 42 are drawn to a method of preparing a medicament but do not recite any positive steps for the same. In the absence of steps for the said method of preparation the claims are rendered indefinite.

Claim 27 recites the terms, 'associated with' or 'characterized by'. In the absence of the specific diseases of this invention, the identity of said diseases associates with or characterized by the presence of pro-inflammatory cytokines would be difficult to define and the metes and bounds of the said diseases applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in this and all other claim(s) in which the said terms have been recited.

Claim 28 is drawn to treatment using a compound of claim 1 but does not recite how it is to be used. This applies to claims 30-31, 34 and 40.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 and 24-35, 40, 42 and 44-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorat-Jacob (WO 97/03700, English Translation; Dcoument B1 in IDS of 03/04/2005) in view of Morel et al (Cytokine, 1996, 8(7), 557-566; Document C2 in IDS of 03/04/2005) and Turnbull et al (WO 93/19096).

Lorat-Jacob, drawn to γ-interferon, teaches agents for the modulation of γ-interferon activity. The agents are of the type A-X-B, wherein A and B are oligosaccharide groups that carry anionic charge to confer affinity for the C-terminal portion of γ-interferon containing the peptide sequence 125-131, and X is a spacer arm connecting A and B via covalent bonds (page 6, lines 5-16). The modulating agent consists of oligosaccharide groups sulfate and/or phosphate groups. The oligosaccharide units A and B contain units that are derived from an N-sulfated osamine or units derived from sulfated uronic acids, notably containing alternating disaccharide units derived from uronic acid as in glycosaminoglycans. The fragments A and B are those preferably obtained from heparan sulfate and can be 6-14 saccharide units long. The spacer X can be any polymer for example polyoside or polyglycol having sufficient length to allow the units A and B to bind to the C-terminal ends of γ-interferon. The polyglycol unit can be a poly(alkylenoxy)arm (page 8). The length of the spacer X can be determined by routine experimentation. In specific embodiments the spacer arm can contain anionic groups like sulfate, phosphate or carboxylic groups and one can also use natural polyosides cellulose, starch, glycosaminoglycans (page 9, lines 1-15). The units A and B can also be fragments obtained from heparin (page 11, lines 1-7).

According to Lorat-Jacob, the agent of his invention can be used as a drug (medicament) to modulate the activity of γ-interferon. It can also be used in combination with γ-interferon (medicament or complex as instantly claimed) comprising vehicles and adjuvants, as a lyophilizate or in the form of an aqueous solution (pages 12-13). However, Lorat-Jacob et al do not exemplify a compound of instant formula (I), wherein the spacer group X is a group as recited in instant claims 7-17 and wherein the saccharide units on either side of the spacer group

are symmetrical. But there is a suggestion of compounds of instant formula (I) comprising saccharide units as in formula (I) and substitutions and spacer groups and their length as recited in instant claims 1-6.

Morel et al, drawn to γ-interferon and the role of heparan sulfate, teach that the concept that cytokine and growth factor activity is governed not only by their bindings to specific cell surface receptors, but also to extracellular components is well accepted and that the interaction of γ-interferon with heparan sulfate/heparin-like molecules result in a tight control of the cytokines (page 564, right column, first full paragraph). This teaching of Morel and the teaching of Lorat-Jacob as explained above, suggests to one of ordinary skill in the art that saccharide oligomers that have heparin or heparan sulfate monomeric units comprising glucosamine units and glucuronic acid units are important for binding to cytokines like γ-interferon in order to modulate their activity.

Turnbull et al, drawn to oligosaccharides, teaches that heparin or heparan sulfate with the complexity and heterogeneity with a large number of different disaccharide units may have different activities and have undesirable side effects and would lack specificity in binding to growth factors on cell surfaces. What is needed is a substantially homogenous preparation of a relatively small molecular compound (page 4, line 38 through page 5, line 13). This means that the structure of the saccharide units in heparin or heparan sulfate should be same or uniform for reducing the side effects and increasing the beneficial activity, i.e., binding to cytokines like γ-interferon by heparin and heparan sulfate fragments that are extracellular components (as taught by Morel above). Hence this is a suggestion to make fragments A and B in the compounds of Lorat-Jacob uniform or symmetrical so that the binding to γ-interferon is the main reaction that

takes place and not any other side reaction that is not beneficial. Lorat-Jacob also suggests that in their compound A-X-B, the fragments A and B may be similar (Lorat-Jacob, page 7, lines last three lines).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make compounds of instant formula (I) and their compositions and complexes with γ-interferon as a medicament for modulating the activity of γ-interferon and thereby treatment of cancers and infectious diseases of viral, bacterial or parasitic origin (Lorat-Jacob page 13, first full paragraph) since such is seen to be taught in the prior art using closely analogous compounds.

One of skill in the art will be motivated to make and use the compounds in the methods of treatment of diseases associated with cytokines like γ-interferon since such compounds having a uniform structure in the carbohydrate fragments is taught in the prior art to have reduced side effects and side reactions and hence would bind only to γ-interferon, thereby achieving better modulation of the γ-interferon activity. This would enhance the beneficial effects of the compounds as instantly claimed.

Response to Applicants Remarks

1. Regarding the rejection of claims 27-34, 38-40, 43 and 45-46 under 35 USC 112, first paragraph maintained in the previous Office action applicants have pointed out to recitations in the specification that applicants believe satisfies the enablement requirement. This is not found to be persuasive. As detailed in the enablement rejection above, the diseases and conditions all have

different etiologies and just inhibiting gamma interferon alone is not seen to be sufficient to treat the diseases and conditions based on the prior art cited.

2. The rejection of claims 8, 30-31 and 40 under 35 USC 112, second paragraph of record in the previous office action, for recitation of the terms, 'for example', has been overcome. The rejection under 35 USC 112, second paragraph is being made of record.

3. Regarding the rejection of claims 1-17, 24-40 and 42-50 under 35 USC 103(a) maintained in the previous Office action applicants argue that:

a) The instant compound of formula (I) has two oligosaccharides fragments that are placed symmetrically with respect to the spacer group X. Lortat-Jacobs fails to teach at least this feature of instant claim 1. The suggestion by Lortat-Jacobs that the groups A and B may be similar does not equate to being symmetrical. The natural molecules and the molecules of the prior art, whether heparin or heparan sulfate, are asymmetrical and do not observe the symmetry of the protein to which they are capable of binding. Lortat-Jacobs also fails to teach or suggest that there should be no sulfate groups in the 3-position in the glucosamine unit of the instant compound.

b) Morel et al (Cytokine) fails to teach the features recited in instant claim 1.

c) Turnbull only appears to describe the composition containing the compound and not the actual structure of the compound. Therefore, the language regarding the uniformity likely relates to the composition instead of the structure.

Applicants' arguments have been considered but are not found to be persuasive.

Lortat-Jacobs teaches agents are of the type A-X-B, wherein A and B are oligosaccharide groups that carry anionic charge to confer affinity for the C-terminal portion of γ-interferon

containing the peptide sequence 125-131, and X is a spacer arm connecting A and B via covalent bonds. The modulating agent consists of oligosaccharides having sulfate and/or phosphate groups. The oligosaccharide units A and B contain units that are derived from an N-sulfated osamine or units derived from sulfated uronic acids, notably containing alternating disaccharide units derived from uronic acid as in glycosaminoglycans. The fragments A and B are those preferably obtained from heparan sulfate and can be 6-14 saccharide units long. Lortat-Jacob may not teach that the polysaccharide units on either side of the spacer are placed symmetrically as instantly claimed. Jacob's teaching points out to the structure of the agent that binds to γ-interferon with the polysaccharides units having the monomeric units found in heparin/ heparan sulfate.

Morel et al, drawn to γ-interferon and the role of heparan sulfate, teaches that the interaction of γ-interferon with heparan sulfate/heparin-like molecules result in a tight spatial control of the cytokines. The reference to spatial control in such binding tells one of skill in the art that the disposition of the two polysaccharide units, i.e. symmetrical or asymmetrical, about the spacer is important. One of ordinary skill in the art will recognize this fact from the teaching of Morel and would modify the disposition of the polysaccharides A and B on either side of the spacer X in the agent taught by Lortat-Jacobs in order to look for agents to which γ-interferon shows high binding affinity.

The term composition in the context recited by Turnbull refers to the component units of the saccharide part and not to a composition comprising the compound. Turnbull also teaches sulfated oligosaccharides such as heparan sulfate and heparin and also teaches about sulfation being only at the 2 and 6-positions (page 7, line 1 through page 8, line 10). This means that the

3-position is not sulfated (as in the proviso in instant claim 1). Since the polysaccharide units from heparin and heparan sulfate that do not have a sulfate at the 3-position have shown promise one of ordinary skill in the art would be motivated to retain the same sulfation pattern.

Conclusion

1. Claims 1-17 and 24-35, 40, 42 and 44-51 are rejected.

2. Claims 18-23, drawn to a process for preparing a compound of formula (II) are seen to be free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
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